Claims

1. A composition which comprises delivery vehicles, said delivery vehicles having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio of the first agent to the second agent which exhibits a non-antagonistic biologic effect to relevant cells in culture or a cell-free system over at least 5% of such concentration range where > 1% of the cells are affected ($f_a > 0.01$) in an *in vitro* assay for biologic effect.

2. A composition which comprises delivery vehicles, said delivery vehicles having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio of the first agent to the second agent which exhibits a non-antagonistic cytotoxic or cytostatic or biologic effect to relevant cells wherein said agents are antineoplastic agents.

3. The composition of claim 2 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range where > 1% of relevant cells are affected ($f_a > 0.01$) in an *in vitro* assay for cytotoxicity.

4. The composition of claim 1 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected ($f_a = 0.1\text{-}0.9$) in said *in vitro* assay.

5. The composition of claim 4 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected ($f_a = 0.2\text{-}0.8$) in said *in vitro* assay.

6. The composition of claim 5 wherein said non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in said *in vitro* assay.

7. The composition of claim 1 which, when administered to a subject, provides a therapeutic activity greater than that which is obtained when said agents are administered in the same ratio but not stably associated with delivery vehicles.

8. The composition of claim 1 wherein said agents are antineoplastic agents.

9. The composition of claim 1 wherein the composition comprises a third agent.

10. The composition of claim 1 wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

11. The composition of claim 10 wherein said vehicles have a mean diameter of less than 250 nm.

12. The composition of claim 1 or 2 wherein said delivery vehicles comprise
liposomes, and/or
lipid micelles, and/or
block copolymer micelles, and/or
microparticles, and/or
nanoparticles, and/or
polymer lipid hybrid systems, and/or
derivatized single chain polymers.

13. The composition of claim 1 wherein said first and second agents are co-encapsulated.

14. The composition of claim 13 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected (f_a = 0.1-0.9) in said *in vitro* assay.

15. The composition of claim 14 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected (f_a = 0.2-0.8) in said *in vitro* assay.

16. The composition of claim 15 wherein said non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in said *in vitro* assay.

17. The composition of claim 2 which, when administered to a subject, provides a therapeutic activity greater than that which is obtained when said agents are administered in the same ratio but not stably associated with delivery vehicles.

18. The composition of claim 2 wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

19. The composition of claim 18 wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M-checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

20. The composition of claim 2

wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or FUDR, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is doxorubicin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

21. A method to prepare a composition comprising delivery vehicles, said vehicles having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio which is non-antagonistic, which method comprises

a) determining in a relevant cell culture assay or cell-free assay for biological activity a mole ratio of said first and second agent which is non-antagonistic over at least 5% of the concentration range over which greater than 1% of cells are affected ($f_a > 0.01$) by said ratio of agents, and

b) encapsulating with said delivery vehicles a mole ratio of agents determined to be non-antagonistic in step a).

22. A method to prepare a composition comprising drug delivery vehicles, said vehicles having stably associated therewith at least a first therapeutic agent and a second therapeutic agent in a mole ratio which is non-antagonistic, which method comprises

a) determining in a relevant cell culture assay or cell-free assay a mole ratio of said first and second agent which is non-antagonistic, wherein said agents are antineoplastic agents, and

b) encapsulating with said delivery vehicles a mole ratio of agents determined to be non-antagonistic in step a).

23. The method of claim 21 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 1%-99% of the cells are affected (f_a = 0.01-0.99) in an *in vitro* assay for cytotoxicity or cytostasis.

24. The method of claim 23 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected (f_a = 0.1-0.9) in an *in vitro* assay for cytotoxicity or cytostasis.

25. The method of claim 24 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected (f_a = 0.2-0.8) in an *in vitro* assay for cytotoxicity or cytostasis.

26. The method of claim 25 wherein said synergistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in an *in vitro* assay for cytotoxicity or cytostasis.

27. The method of claim 22 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that > 1% of the cells are affected (f_a > 0.01) in an *in vitro* assay for cytotoxicity or cytostasis.

28. The method of claim 27 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected (f_a = 0.1-0.9) in an *in vitro* assay for cytotoxicity or cytostasis.

29. The method of claim 28 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected (f_a = 0.2-0.8) in an *in vitro* assay for cytotoxicity or cytostasis.

30. The method of claim 29 wherein said synergistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in an *in vitro* assay for cytotoxicity or cytostasis.

31. The method of claim 21, wherein said determining employs testing at least one ratio of said agents at a multiplicity of concentrations and applying an algorithm to calculate a synergistic, additive, or antagonistic effect for said ratio over a range of concentrations.

32. The method of claim 31 which employs testing a multiplicity of ratios.

33. The method of claim 31 wherein said algorithm is the Chou-Talalay median effect method.

34. The method of claim 31 wherein said agents are antineoplastic agents.

35. The method of claim 22 wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

36. The method of claim 22 wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M-checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

or wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

37. The method of claim 27

wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is adriamycin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

38. A composition prepared by the method of claim 21.

39. A composition prepared by the method of claim 22.

40. A composition prepared by the method of claim 31.

41. A method to treat a disease condition in a subject which method comprises administering to a subject in need of such treatment a therapeutically effective amount of the composition of claim 1.

42. A method to treat a disease condition in a subject which method comprises administering to a subject in need of such treatment a therapeutically effective amount of the composition of claim 2.

43. A method to treat a disease condition in a subject which method comprises administering to a subject in need of such treatment a therapeutically effective amount of the composition of claim 38.

44. A method to treat a disease condition in a subject which method comprises administering to a subject in need of such treatment a therapeutically effective amount of the composition of claim 39.

45. The method of claim 41 wherein the subject is a human.

46. The method of claim 41 wherein the subject is a non-human mammal or avian.

47. The method of claim 42 wherein the subject is a human.

48. The method of claim 42 wherein the subject is a non-human mammal or avian.

49. A method to treat a disease condition in a subject which method comprises administering to a subject in need of such treatment a therapeutically effective amount of a first composition comprising delivery vehicles stably associated with at least a first therapeutic agent

and a second composition comprising delivery vehicles stably associated with at least a second therapeutic agent,

wherein the delivery vehicles in said first and second composition are coordinated with respect to pharmacokinetics; and

wherein said administering is at a ratio of first therapeutic agent to second therapeutic agent that is non-antagonistic.

50. The method of claim 49 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 1%-99% of the cells are affected (f_a = 0.01-0.99) in an *in vitro* assay for cytotoxicity or cytostasis.

51. The method of claim 50 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected (f_a = 0.1-0.9) in an *in vitro* assay for cytotoxicity or cytostasis.

52. The method of claim 51 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected (f_a = 0.2-0.8) in an *in vitro* assay for cytotoxicity or cytostasis.

53. The method of claim 52 wherein said synergistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in an *in vitro* assay for cytotoxicity or cytostasis.

54. A kit for treatment of a subject which kit comprises

in a first container a composition comprising delivery vehicles stably associated with at least one first therapeutic agent;

in a second container a second composition comprising delivery vehicles stably associated with at least a second therapeutic agent;

wherein the delivery vehicles in said first and second compositions are coordinated with respect to pharmacokinetic behavior; and

wherein said kit further contains instructions for administering said first and second composition at ratios of said first and second therapeutic agent that are non-antagonistic and/or wherein the amounts of said first and second compositions in said containers is proportional to a

ratio of said first and second therapeutic agent that is non-antagonistic and/or said containers are calibrated to dispense amounts of said first and second composition wherein the ratio of first and second therapeutic agents is non-antagonistic.

55. The kit of claim 54, wherein the containers are syringes.